2017 Update on

MDS

MPN

Overlap Neoplasms

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2016 WHO Classification Scheme for Myeloid Neoplasms

Acute
- Acute Myeloid Leukemia
  - Myelodysplastic Syndromes
    - MDS/MPN
      - Myeloproliferative Neoplasms
        - Chronic Myeloid Leukemia
          - Polycythemia Vera
          - Essential Thrombocythemia
          - Primary Myelofibrosis
          - Chronic Neutrophilic Leukemia
          - Chronic Eosinophilic Leukemia, NOS
          - Mastocytosis
          - MPNs, unclassifiable
      - MDS/MPN, unclassifiable
        - MDS/MPN with ring sideroblasts and thrombocytosis
          - (MDS/MPN-RS-T)
        - MDS/MPN, unclassifiable
          - (MDS/MPN-U)
      - Atypical Chronic Myeloid Leukemia (aCML)
      - Juvenile Myelomonocytic Leukemia (JMML)
  - MDS/MPN
    - Myelodysplastic Syndromes
      - MDS/MPN
        - Myeloproliferative Neoplasms
          - Chronic Myeloid Leukemia
            - Polycythemia Vera
            - Essential Thrombocythemia
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          - (MDS/MPN-U)

Chronic
- Acute Myeloid Leukemia
  - Myelodysplastic Syndromes
    - MDS/MPN
      - Myeloproliferative Neoplasms
        - Chronic Myeloid Leukemia
          - Polycythemia Vera
          - Essential Thrombocythemia
          - Primary Myelofibrosis
          - Chronic Neutrophilic Leukemia
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      - MDS/MPN, unclassifiable
        - MDS/MPN with ring sideroblasts and thrombocytosis
          - (MDS/MPN-RS-T)
        - MDS/MPN, unclassifiable
          - (MDS/MPN-U)

Myeloid or lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2
Features of MDS and MPN

- **MDS**
  - Ineffective hematopoiesis
  - Low blood counts (anemia most common)
  - Abnormal blood cell morphology (dysplasia)

- **MPN**
  - "Super"-effective hematopoiesis
  - Increased blood counts
  - Dysplasia absent
MDS / MPN:
An Overlap Neoplasm

Dysplasia
Ineffective hematopoiesis

Proliferation
Effective hematopoiesis

MDS
RCUD
RARS
RCMD
RAEB
Del (5q)
MDS-U

MDS/MPN
CMML
JMML
aCML
MDS/MPN-RS-T
MDS/MPN-U

MPN
PV
ET
MF
CML
CEL
CNL
MPN-U

Effective hematopoiesis
Ineffective hematopoiesis

RCMD
RAEB
MDS-U
Some Things Shouldn’t Overlap
## 2016 World Health Organization Classification of MDS

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)³</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors wiring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>Cytopenia(s), &lt;1 x 10⁹/L monocytes</td>
<td>Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts-1 (MDS-EB-1)</td>
<td>Cytopenia(s), ≤2%–4% blasts, &lt;1 x 10⁹/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods</td>
</tr>
<tr>
<td>MDS with excess blasts-2 (MDS-EB-2)</td>
<td>Cytopenia(s), 5%–19% blasts, &lt;1 x 10⁹/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods</td>
</tr>
<tr>
<td>MDS, unclassifiable (MDS-U)</td>
<td>Cytopenias, ±1% blasts on at least 2 occasions</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>Cytopenias, &lt;2% blasts</td>
<td>Dysplasia in 1–3 lineages, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts in transformation (MDS-EB-T)²</td>
<td>Cytopenias, 5%–19% blasts</td>
<td>Multilineage dysplasia, 20%–29% blasts, ± Auer rods</td>
</tr>
</tbody>
</table>
MDS: Revised International Prognostic Scoring System (IPSS-R)

calculate risk score

cytogenetic risk group

- very good
- good
- intermediate
- poor
- very poor

- del(11q), -Y
- normal, del(20), del(5q) alone or with other anomaly, del(12p)
- +8, del(7q), i(17q), +19, +21, any single or double abnormality not listed,
two or more independent clones
der(3q), -7, double with del(7q), complex with 3 abnormalities
complex with > 3 abnormalities

Bone marrow blast %

- ≤ 2%
- > 2% - < 5%
- 5% - 10%
- > 10%

Hemoglobin (g/dL)

- ≥ 10
- 8 - < 10
- < 8

Platelet count (x 10^9/L)

- ≥ 100
- 50 - < 100
- < 50

Absolute neutrophil count (x 10^9/L)

- ≥ 0.8
- < 0.8

assign IPSS-R risk group

<table>
<thead>
<tr>
<th>total score</th>
<th>% of patients</th>
<th>median survival, years</th>
<th>time to 25% with AML, years</th>
<th>IPSS-R risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>19%</td>
<td>8.8</td>
<td>not reached</td>
<td>very low</td>
</tr>
<tr>
<td>&gt; 1.5 - 3</td>
<td>38%</td>
<td>5.3</td>
<td>10.8</td>
<td>low</td>
</tr>
<tr>
<td>&gt; 3 - 4.5</td>
<td>20%</td>
<td>3</td>
<td>3.2</td>
<td>intermediate</td>
</tr>
<tr>
<td>&gt; 4.5 - 6</td>
<td>13%</td>
<td>1.6</td>
<td>1.4</td>
<td>high</td>
</tr>
</tbody>
</table>

Overall survival, years

Patients, %

Time to AML evolution, years

Patients, %
## 2016 World Health Organization Classification of MDS/MPN

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMML-0</strong></td>
<td>&gt;1000 monocytes/ul &lt;2% blasts</td>
<td>Dysplasia in &gt;1 cell line, &lt;5% blasts</td>
</tr>
<tr>
<td><strong>CMML-1</strong></td>
<td>&gt;1000 monocytes/ul 2-4% blasts</td>
<td>Dysplasia in &gt;1 cell line, 5-9% blasts</td>
</tr>
</tbody>
</table>
What is ‘Dysplasia’?
Red Blood Cell (Erythroid) Dysplasia (Dyserythropoiesis)

<table>
<thead>
<tr>
<th>Blood</th>
<th>Marrow iron stain</th>
<th>Red blood cell precursors in the marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro-ovalocytes</td>
<td>Ring sideroblasts</td>
<td></td>
</tr>
</tbody>
</table>

![Blood](image1)

![Marrow iron stain](image2)

![Red blood cell precursors in the marrow](image3)
White Blood cell dysplasia (Dysgranulopoiesis)

- Hypogranularity
- Hypolobation
- Hyperlobation
- Pseudo-Pelger Huet cells

![Normal neutrophil]

![Hyperlobation]

![Pseudo-pelger Huet; hypolobation]

![Hypogranularity]
Megakaryocyte/platelet dysplasia (Dysmegakaryopoiesis)

- Micro/dwarf megakaryocytes
- Hypolobation; separate nuclear lobes
- Platelets - giant, bizarre, hypogranular

- Large, hypogranular platelets
- Hypolobated megakaryocyte
- Dwarf megakaryocytes
Monocytes in CMML

Peripheral Blood

Bone Marrow Aspirate
Mutations in MDS/MPN
How Certain Mutations May ‘Tip the Scales’ Toward MPN vs. MDS

Vainchenker Kralovics, *Blood*, 2017
Mutational Landscape of MDS/MPN

- **CMML**
  - $TET2$, $SRSF2$, $ASXL1$, $RUNX1$, $JAK2$
  - $N/K - RAS$

- **Atypical CML**
  - $SETBP1$, $JAK2$, $N/K - RAS$, $ASXL1$, $CSF3R$

- **JMML**
  - $RAS$ pathway: $PTPN11$, $N/K - RAS$, $CBL$, $NF1$

- **MDS/MPN - RS**
  - $SF3B1$, $JAK2$, $MPL$

- **Mughal et al, Haematologica, 2015**
MDS/MPN-RS-T (RARS-T): Mutational Pathogenesis

Somatic mutation of *SF3B1* determining mitochondrial iron overload and ineffective erythropoiesis

Somatic mutation of *JAK2* or *MPL* determining gain of signaling and thrombocytosis

Normal hematopoietic cell → Ring sideroblasts and ineffective erythropoiesis (myelodysplastic features of RARS) → Ring sideroblasts and thrombocytosis (myelodysplastic & myeloproliferative features of RARS-T)

From Cazzola et al, Hematology Am Soc Hematol Educ Program, 2011
Prognosis in MDS/MPN
# Prognostic Factors in CMML

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome and hazard ratio (HR) (P value)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts ≥ 10%</td>
<td>Overall survival, HR 1.8 (P &lt; .0001)</td>
<td>This parameter separates CMML-1 (BM blasts &lt; 10%) from CMML-2 (BM blasts 10%-19%).</td>
</tr>
<tr>
<td>WBC count ≥ 13 × 10⁹/L</td>
<td>Overall survival, HR 2.6 (P &lt; .0001) and progression to AML, HR 2.9 (P &lt; .0001)</td>
<td>This parameter separates myelodysplastic-like CMML (WBC &lt; 13 × 10⁹/L) from myeloproliferative-like CMML (WBC ≥ 13 × 10⁹/L).</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 10 g/dL</td>
<td>Overall survival, HR 1.5 (P &lt; .0001)</td>
<td>Severe anemia may reflect clonally advanced myeloid neoplasm.</td>
</tr>
<tr>
<td>CMML-specific cytogenetic risk†</td>
<td>Overall survival, HR 1.7 (P &lt; .0001)</td>
<td>Abnormalities of chromosome 7 and complex karyotype represent negative prognostic factors in myeloid neoplasms.</td>
</tr>
<tr>
<td>Platelet count &lt; 100 × 10⁹/L</td>
<td>Overall survival, HR 2.1 (P &lt; .0001)</td>
<td>Thrombocytopenia may reflect clonally advanced myeloid neoplasm.</td>
</tr>
</tbody>
</table>

## CMML Prognostic Model: Bone Marrow Blast % and WBC Count

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Overall Survival (Months) n=386</th>
<th>Overall Survival (Months) CMML/MDS n=204</th>
<th>Overall Survival (Months) CMML/MPN n=182</th>
<th>P-value</th>
<th>AML Progression at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMML-0</td>
<td>31</td>
<td>48</td>
<td>17</td>
<td>.03</td>
<td>7%</td>
</tr>
<tr>
<td>&lt;5% blasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMML-I</td>
<td>19</td>
<td>29</td>
<td>15</td>
<td>.008</td>
<td>18%</td>
</tr>
<tr>
<td>5-9% blasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=204</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMML-2</td>
<td>13</td>
<td>17</td>
<td>10</td>
<td>.09</td>
<td>36%</td>
</tr>
<tr>
<td>10-19% blasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=81</td>
<td></td>
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</tr>
</tbody>
</table>

*WBC ≤ vs >13,000 (CMML/MDS vs CMML/MPN)

Schuler et al, Leuk Res 2015
CMML Prognostic Scoring System

**Graphs E and F**

- **Graph E** shows survival curves for different risk groups over time.
- **Graph F** also shows survival curves, with different risk groups indicated.

**Legend**

- **Absence**
  - Leucocytosis (>15)
  - Age (>65)
  - Anemia
  - Thrombocytopenia (<100)
  - ASXL1 mutation

- **Presence**
  - Leucocytosis (>15)
  - Age (>65)
  - Anemia
  - Thrombocytopenia (<100)
  - ASXL1 mutation

**Scoring System**

- Low < 4
- Intermediate 4-8
- High >8

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**SETBP1** Mutation in Atypical CML

- **WBC (p=0.008)**
- **Hb (p=0.44)**
- **Platelets (p=0.16)**

**SETBP1**- = 77 months  
**SETBP1**+ = 22 months  

p=0.01, HR=2.27

Piazza R. et al, Nat Genetics 2013
Atypical CML: Disease Course

- The largest series of WHO-defined aCML: 55 cases from an Italian cohort.¹

- **Overall median survival**: 25 months compared with survivals ranging from 14 to 30 months from 3 smaller studies.²-⁴

- **Transformation to AML** occurred in 22 patients (40%), with a median time from diagnosis of 18 months in the Italian study.¹

- **Predictors of shorter survival**: older age (>65 years), female gender, WBC count (>50x10⁹/L), and presence of immature circulating cells.¹

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¹ Breccia et al, Haematologica, 2006
² Kurzrock et al, J Clin Oncol, 2001
³ Martiat et al, Blood, 1991
⁴ Hernandez et al, Ann Oncol, 2000
Clinical Management
Goals of Therapy in MDS/MPN

- Cure
- Reduction of symptoms / splenomegaly
- Improvement of blood counts
- Cytogenetic / molecular remission
- Avoidance of disease progression / AML
Common Clinical Issues in MDS/MPN

MPN

- WBC count (leukocytosis)
- Platelet count (thrombocytosis)

MDS

- Red blood cell count (anemia)

Progression to AML
A 68 year-old man presents with a 6-month history of progressive fatigue. His CBC shows the following:

- White blood cell count: 5,800/ul (normal: 4,000-11,000/ul)
- Hemoglobin/hematocrit: 8.4 g/dL / 27% (normal ~ 15 g/dL; 45%)
- Platelets: 620,000/ul (normal: 150,000-400,000/ul)

A peripheral blood smear is reviewed and a bone marrow biopsy is performed.
Case (continued)

Peripheral blood:
- Increased platelets & dysplastic neutrophil

BM aspirate:
- Increased clustered megas
- Dysplastic erythroids
- Ring sideroblasts

Cytogenetics: normal
Myeloid mutation panel: **SF3B1 & JAK2 V617F**

Diagnosis: MDS/MPN-RS-T

From Cazzola et al, Hematology Am Soc Hematol Educ Program, 2011
Conventional Medications for MDS/MPN

To improve anemia
- EPO +/- G-CSF
- Lenalidomide for intermediate- to high-risk disease and/or concern for evolution to AML
- Hypomethylating agents: Azacitidine or decitabine
- Hematopoietic stem cell transplantation

Supportive Care
- RBC and platelet transfusions
- Antibiotics
- Iron chelation

To control leukocytosis, thrombocytosis, and splenomegaly
- Hydroxyurea
- PEG-Interferon-a
- Anagrelide
Summary of Phase I/II Trials of Hypomethylating Therapy in CMML

- **Overall response rate:** 25-70% (usually ~30-40%)
- **Complete remission rate:** 10-58%
- **Overall Survival (OS):** 12-37 months

Prognostic factors for OS in pts treated with azacitidine

- **Worse OS:** BM blasts >10% and WBC >13 x 10^9/L
- **Better OS:** Absolute monocyte count <10 x 10^9/L and PB blasts <5%

---

2 Ades *et al*, *Leuk Res*, 2013
3 Fianchi, *et al*, *Leuk Lymphoma*, 2013
Transplantation in CMML

- No randomized trials
- Increasing use of reduced intensity conditioning
  - Other donor sources: haploidentical; double umbilical cord units

**FHCRC** (n=85)¹
- 10-yr overall and relapse-free survival: 40% an 38%, respectively
- Increasing age, higher SCT co-morbidity index, and poor-risk cytogenetics were associated with increased mortality and reduced relapse-free survival

**EBMT** (n=513; 95 pts with sAML)²
- 4-year overall and relapse-free survival: 33% and 27%, respectively
- In multivariate analysis, the only significant prognostic factor for survival was the presence of a complete remission at time of transplantation

¹Eissa H et al, Biol Blood Bone Marrow Transplant, 2011
²Symeonidis et al, Br J Haematol, 2015
## Targeted Therapy Considerations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Therapy</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK2 V617F</strong></td>
<td>JAK inhibitor</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td><strong>CSF3R T618I</strong></td>
<td>JAK inhibitor</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td><strong>RAS pathway (e.g. PTPN11, RAS, CBL, NF1)</strong></td>
<td>MEK inhibitor</td>
<td>Trametinib</td>
</tr>
<tr>
<td><strong>SF3B1</strong></td>
<td>TGF-B ligand trap</td>
<td>Luspatercept</td>
</tr>
<tr>
<td>Other splicing gene mutations</td>
<td>Splicing modulator</td>
<td>H3B-8800</td>
</tr>
<tr>
<td>(e.g. SRSF2)</td>
<td>IDH 1/2 inhibitor</td>
<td>Enasidinib</td>
</tr>
<tr>
<td><strong>IDH 1/2</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults

Michael R. Savona,¹ Luca Malcovati,² Rami Komrokji,³ Ramon V. Tiu,⁴ Tariq I. Mughal,⁵ Attilio Orazi,⁶ Jean-Jacques Kiladjian,⁷ Eric Padron,³ Eric Solary,⁸ Raoul Tibes,⁹ Raphael Itzykson,⁷ Mario Cazzola,² Ruben Mesa,⁹ Jaroslaw Maciejewski,⁴ Pierre Fenaux,⁷ Guillermo Garcia-Manero,¹⁰ Aaron Gerds,⁴ Guillermo Sanz,¹¹ Charlotte M. Niemeyer,¹² Francisco Cervantes,¹³ Ulrich Germing,¹⁴ Nicholas C. P. Cross,¹⁵ and Alan F. List,³ on behalf of the MDS/MPN International Working Group

¹Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center, TN; ²University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ³H. Lee Moffitt Cancer Center, Tampa, FL; ⁴Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; ⁵Tufts University Medical Center, Boston, MA; ⁶Weill Cornell Medical College, New York, NY; ⁷Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Université Paris Diderot, Paris, France; ⁸Institut Gustave Roussy, Villejuif, France; ⁹Mayo Clinic Cancer Center, Scottsdale, AZ; ¹⁰MD Anderson Cancer Center, Houston, TX; ¹¹Hospital Universitario y Politécnico La Fe, Valencia, Spain; ¹²University of Freiburg, Germany; ¹³The August Pi i Sunyer Biomedical Research Institute, University of Barcelona, Barcelona, Spain; ¹⁴University of Düsseldorf, Düsseldorf, Germany; and ¹⁵University of Southampton and Wessex Regional Genetics Laboratory, Salisbury, United Kingdom
MDS/MPN: Summary

• Clinical, laboratory, pathology, and genetic features are used to diagnose MDS/MPN and its subtypes

• The combination of increased WBC and/or platelet counts with anemia can make treatment decisions challenging; hypomethylating agents are commonly employed

• For younger patients with higher-risk disease and an acceptable co-morbidity index, allogeneic HSCT is the preferred treatment

• Searching for actionable mutations may provide opportunities for targeted therapy; accrual in clinical trials is highly recommended for these rare diseases
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Community of MPN Investigators
Our Patients & Their Caregivers

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